CIGB CENTRO DE INGENIERÍA GENÉTICA Y BIOTECNOLOGÍA

Ave.31, e/ 158 y 196,
Cubanacán, Playa, La Habana, Cuba
Teléfono: 72716022

www.cigb.edu.cu LinkedIn: CIGBCuba Twitter: CIGBCuba Facebook: CIGBCubaCuba

Heberprot-P ®

A product containing recombinant human epidermal growth factor that directly infiltrates the bed of diabetic foot ulcers (UPD) to stimulate new granulation tissue and wound healing in diabetic foot ulcers

DESIGN AND EDITING:

Communication Group of Center for Genetic Engineering and Biotechnology; 2021 **Center for Genetic Engineering and Biotechnology** A distinctive company of the Cuban biotechnology, which develops, produces, markets and exports innovative products for key areas of the biomedical, veterinary, agricultural, aquaculture and industrial sectors, for one health. It has a portfolio of research and development (R&D) projects and products, protected by patents. Its more than 30 products marketed in more than 35 countries, include leading and only drugs of its kind, to treat diseases with no other effective therapeutic solutions. Several medications are inserted into national programs to provide a comprehensive system of health care. The staff of the CIGB works with social responsibility and harmony with the environment.

DIABETIC FOOT ULCER TREATMENT

The therapeutic management of patients with a diabetic foot ulcer (DFU) is currently based on:

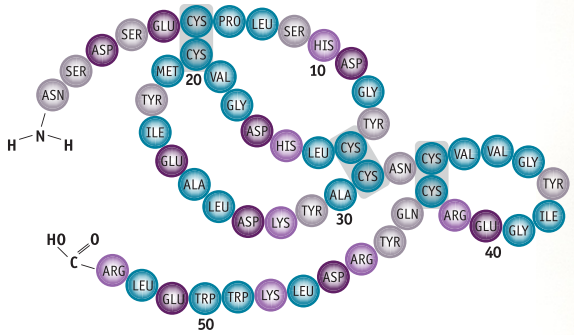
- Relief of pressure.
- Restoring skin perfusion.
- Treating and controlling infection.
- Metabolic control.
- Co-morbidity managements.
- Local wound care:

-Examine ulcer evolution frequently.
-Debride the ulcer.
-Select good ulcer care procedure according to international approved by medical standards.
-Prevention of recurrence.

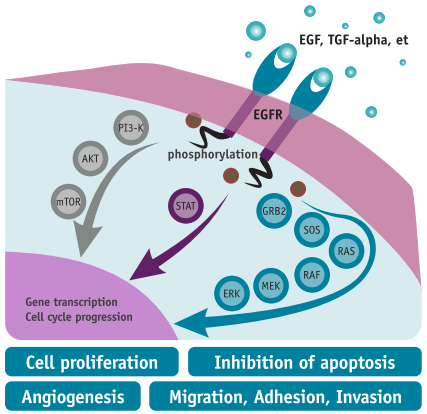
- Provide effective patient and family education.

EPIDERMAL GROWTH FACTOR, A REPLACEMENT THERAPY TO TREAT DIABETIC FOOT ULCER

Epidermal growth factor (EGF) is a 53 amino acid polypeptide isolated for the first time from mice submaxillary glands by Stanley Cohen. It stimulates fibroblasts, keratinocytes and vascular endothelial cells proliferation that improve high quality new granulation tissue and wound healing. The healing mechanisms start with the coupling of EGF with specific receptors located on the cellular membrane.



EGF receptors are glycoproteins with an extracellular binding domain, a transmembrane region and a cytoplasmic portion with tyrosine kinase activity. EGF receptors are expressed on most human cell types including those that play critical roles in wound repair such as fibroblasts, endothelial cells and keratinocytes.

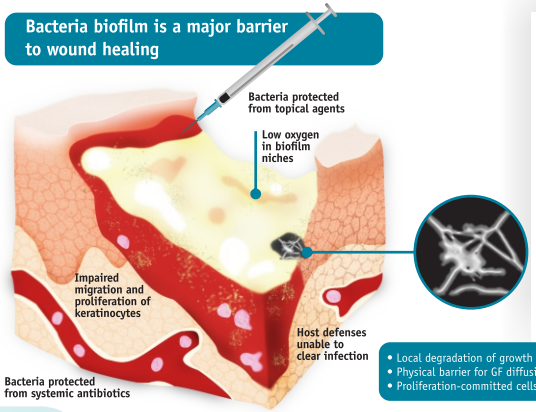


THE RATIONALE OF EGF USE TO TREAT DIABETIC FOOT ULCERS

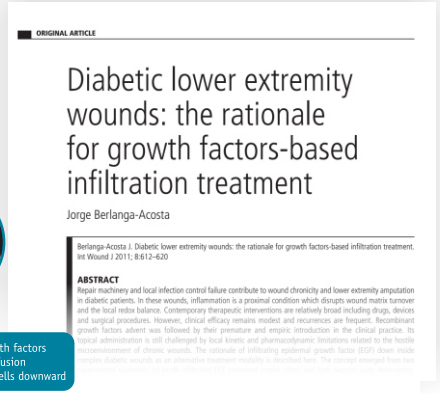
- Impairment of healing in diabetic patients, associated with a relative deficit of growth factors (EGF among them).
- Role of EGF in stimulating not only angiogenesis but also cell division, differentiation and migration in damaged tissues and wounds.

WHY EGF HAS TO BE INTRALESIONALLY INJECTED?

- The availability of the growth factor at wound surface is limited.
- Bacterial biofilm is a physical barrier that limit and affect added healing medications with cell receptors.
- Wound area is rich in acute proteases that can degrade quite fast any added healing medication.
- Cells at the deep tissue layers are richer in EGF receptors when compared with epidermal and surface cell tissues.



- Local degradation of growth factors
- Physical barrier for GF diffusion
- Proliferation-committed cells downward


ORIGINAL ARTICLE

Diabetic lower extremity wounds: the rationale for growth factors-based infiltration treatment

Jorge Berlanga-Acosta

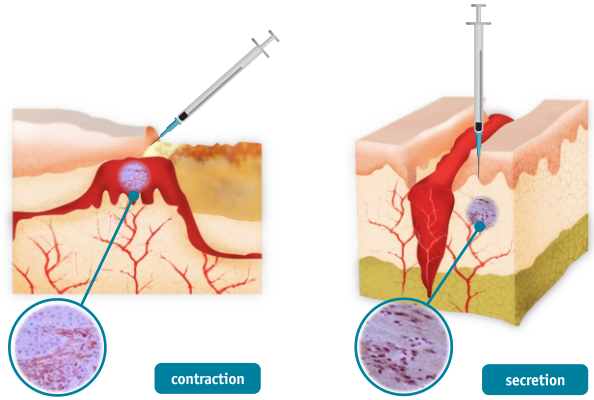
Berlanga-Acosta J. Diabetic lower extremity wounds: the rationale for growth factors-based infiltration treatment. Int Wound J 2011; 8:612–620

ABSTRACT

Repair machinery and local infection control failure contribute to wound chronicity and lower extremity amputation in diabetic patients. In these wounds, inflammation is a proximal condition which disrupts wound matrix turnover and the local redox balance. Contemporary therapeutic interventions are relatively broad including drugs, devices and surgical procedures. However, clinical efficacy remains modest and recurrences are frequent. Recombinant growth factors advent was followed by their premature and empiric introduction in the clinical practice. Its topical administration is still challenged by local kinetic and pharmacodynamic limitations related to the hostile microenvironment of chronic wounds. The rationale of infiltrating epidermal growth factor (EGF) down inside complex diabetic wounds as an alternative treatment modality is described here. The concept emerged from two

WHERE TO INJECT EGF?

Injecting EGF deep into the wound base and contours would allow larger pharmacodynamics response in terms of high quality and faster new granulation tissue formation and as consequence better and faster wound closure.



KEY FACTS OF INFILTRATION METHODOLOGY

- Deposit t EGF in the wound deep extracellular matrix.
- Reduce EGF exposition to the superficial bacterial biofilm avoiding in parallel proteolysis due to prolonged acute protease expositions released at wound surfaces.
- Favor an adequate local EGF access to cells at the deep tissue layers that are richer in EGF receptors when compared with epidermal and surface cell tissues
- Stimulate the ascending granulation and the contraction of wound by mimicking natural wound healing process.

CLINICAL TRIALS AND POST MARKETING EXPERIENCE

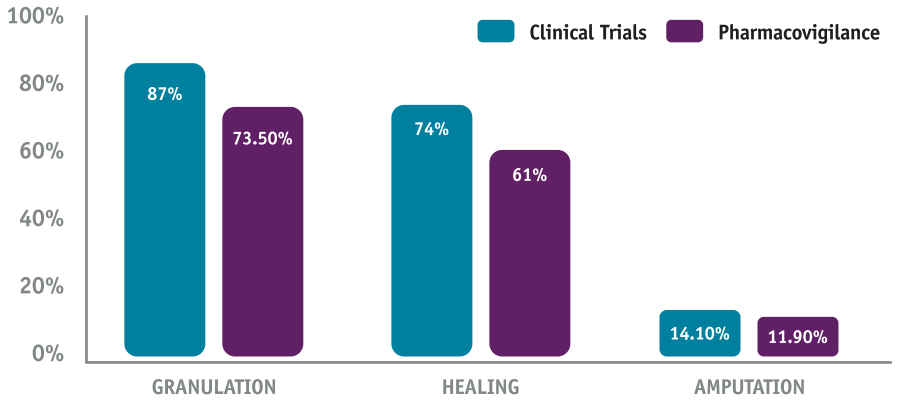
Exploratory and confirmatory clinical trials have been completed in patients with advanced DFU and high amputation risk (reviewed in reference 4).

Properties and advantages of Heberprot-P®

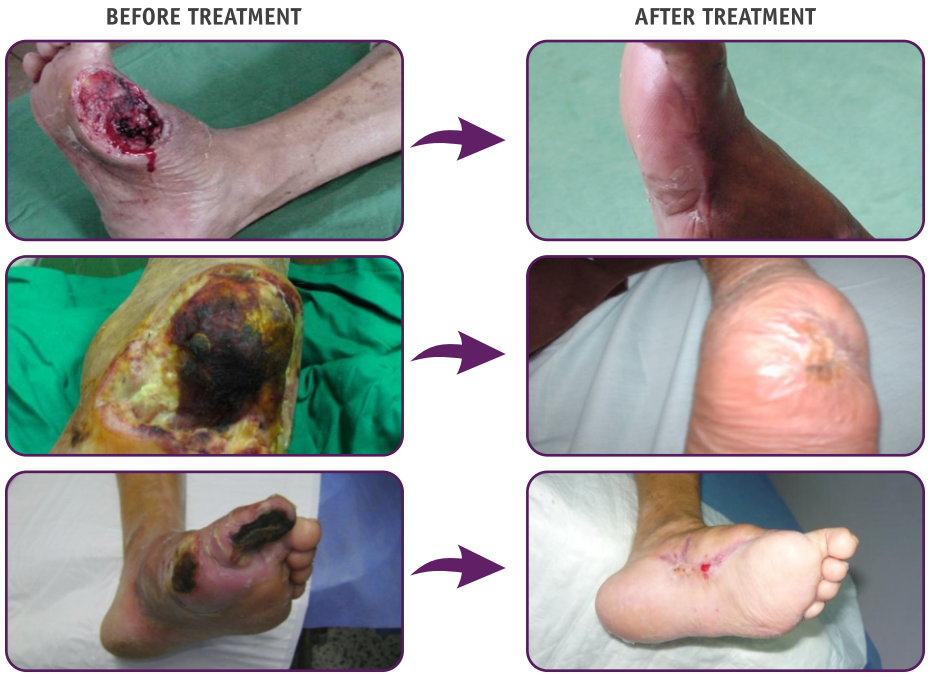
- Stimulates the development of new granulation tissue accelerating re-epithelization, scar formation and wound healing in diabetic foot ulcers.
- Reduces time for healing.
- Reduces risk of amputation.

Post marketing active surveillance was initiated to evaluate drug effectiveness and safety.

EFFICACY RESULTS IN CLINICAL TRIALS (POOLED) AND PHARMACOVIGILANCE EXPERIENCES OF HEBERPROT-P ® (INTRALESIONAL rhEGF) IN PATIENTS WITH DFU



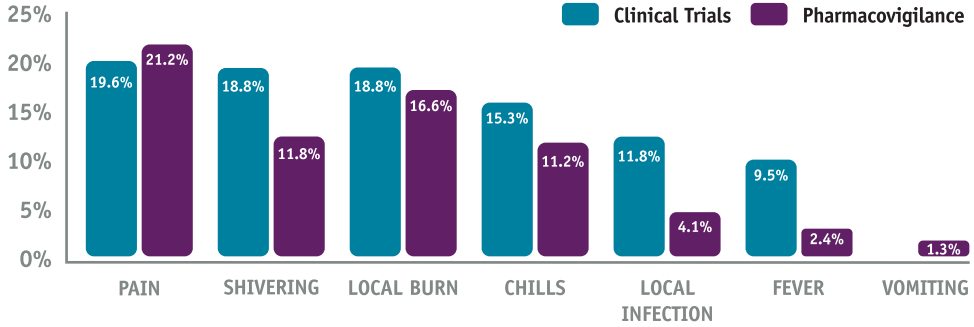
LESIONS TREATED WITH HEBERPROT-P ®



OVERVIEW OF SAFETY

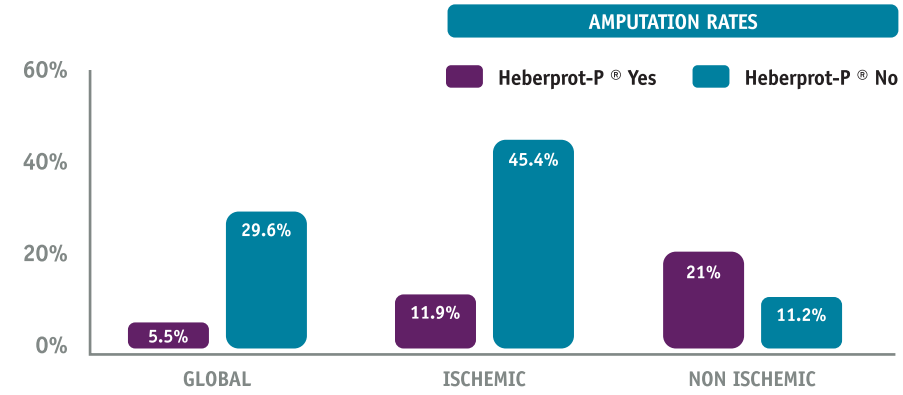
Most frequent adverse events pharmaco-surveillance

Recombinant EGF when applied on diabetic ulcers have been well tolerated showing a safe profile. Around half of the patients (63.1% in the clinical trials and 46.2% in the post marketing) reported of adverse event.



IMPACT STUDIES IN CUBA

Three observational, retrospective and descriptive epidemiological studies were carried out in 8 Cuban hospitals. The objective was to evaluate the benefits of **Heberprot-P®** treatment in the patient outcomes, regarding major amputations. As shown in the figure below, groups of patients treated with **Heberprot-P®** evidenced a low amputation rate of 5.5%. Compared to groups not treated with the treatment but only with general standard care showing higher amputation rates, 29.6%.



HEBERPROT-P ® 75

Please read carefully the leaflet included in the box.

Heberprot-P® is a formulation containing recombinant human epidermal growth factor (rhEGF) for intralesional administration of diabetic foot ulcers. EGF infiltration facilitates its coupling to EGF cells receptors activating the phosphorylation of kinase enzymes associated in switching off cell catabolic pathways activating anabolism. As a therapy the process is unique, because is able to mimic the biological scenario of a non-diabetic person performing high quality and fast cell division, migration and differentiation. The rhEGF is purified from a transformed Saccharomyces cerevisiae yeast strain and presented as a lyophilized preparation containing 75 µg of rhEGF per vial.

Composition: Each vial contains rhEGF (active ingredient), Sucrose, Dextran 40 and buffer phosphate.

Administration route: Parenteral administration through the intralesional route.

Storage conditions: Store at 4°C to 8°C.

Shelf live: 36 months. Expiration date is indicated on the label and package.

Indication: For use only under MEDICAL PRESCRIPTION.

Heberprot-P® is indicated, along with other conventional therapies, to treat diabetic patients holding neuropathic and ischemic ulcers. The therapy is recommended to treat stages 3 and 4 ulcers of Wagner classification with an area larger than 1 cm2. When applied as described, it is able to stimulate the formation of useful granulation tissue improving and speeding second intention healing which also could be boosted through skin auto graft.

Contraindications:

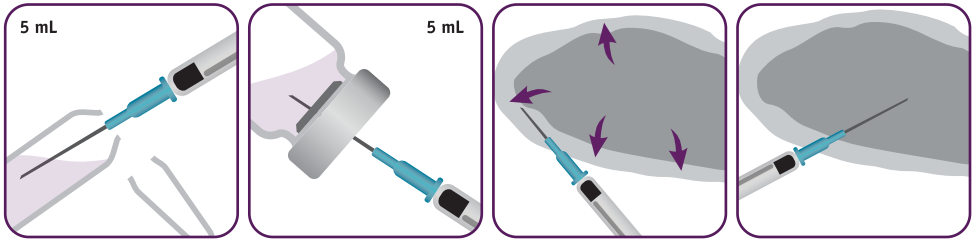
- In patients with a background of hypersensitivity either to the product, or any of its components.
- In patients with acute cardiovascular events as: acute heart attack, severe angina, acute stroke or transitory ischemia or thromboembolic events in the two previous months.
- In patients with severe congestive heart inadequacy (NYHA III and IV), severe auricule-ventricular block (grade III) and auricular fibrillation with uncontrolled rhythm.
- In patients with personal history or suspicion of malignant illnesses.
- In patients with diabetic coma or diabetic ketoacidosis.

Precautions: The administration of biological products must be done carefully and take the necessary provisions in case of unexpected adverse events. Before using **Heberprot-P®**, coexistent conditions, such as: infection and osteomyelitis must be treated. In patients with ischemia due to peripheral macroangiopathy some reperfusion procedure of the affected limb should be performed. It is not known whether **Heberprot-P®** is excreted in maternal milk. Its use in nursing mothers is not recommended. Until now, there is not sufficient information that supports its use in pregnant women and pediatric patients, so doctors must perform a risk/benefit balance in every case.

Administer with caution in patients with a history of acute cardiovascular events such as myocardial infarction, stroke or transient ischemia or thromboembolism, in patients with clinically significant valve disease (i.e. calcified aortic valves), severe hypertension and history of venous thrombosis.
It is necessary to administer with precaution in patients with renal failure with creatinine higher than 200 µmol/L, in such cases doctors must perform a risk/benefit balance.
Whenever infection is present it is necessary to treat it early and appropriately, before using **Heberprot-P®**.

Posology and Method of Administration:

- **Heberprot-P®** improves its therapeutic effects when combined with the appropriate standard care of diabetic foot ulcer, consisting in suitable lesion debridement, pressure offloading of susceptible zones and regular cures. It is necessary to make the diagnosis to apply as soon as possible a suitable treatment to control ulcer infection before using **Heberprot-P®**. In lesions where malignancy is suspected, before using **Heberprot-P®**, it is necessary to perform a biopsy to exclude the presence of malignant cells.
- **Heberprot-P®** is a lyophilized formulation of 75 µg of EGF that has to be diluted in 5 mL of water for injection or 0.9 % saline solution before administration.
- **Heberprot-P®** is administered 3 times per week by intralesional route until complete granulation is achieved during a maximum of 8 weeks waiting later for a total wound closure either by natural healing process or by skin grafting.
- The treatment should be discontinued once useful granulation tissue covers the whole lesion or after achieving a wound area reduction to less than 1 cm2.
- After the cure is done, infiltrations proceed at the ulcer edges using 26 G x ½" needles. In case of deep lesions, to inject **Heberprot-P®** at the wound bottom either 24 G x 1½" or 24 G x ¾" needles are recommended.
- The reconstituted vial should be administered applying 0.5 mL/shot about 0.5 cm deep into the ulcer.
- First, infiltrate the cleanest areas of the lesions, moving later to the infected ones. To avoid extending infection to wound clean areas, please consider changing needles in the different sites of puncture. This procedure will help to prevent germ transmission from one place to another.
- Afterwards, cover the lesion with dressing gauze dampened with saline solution in order to maintain a wet and clean environment.



- If after 3 weeks of uninterrupted treatment no useful granulation tissue has begun to develop at ulcer bed, it is necessary to re-evaluate the treatment and consider other factors that could affect healing, such as osteomyelitis, local infection and metabolic unbalance.

Presentation:
The product is available in:
- Box x 1 vial containing 75 µg of lyophilized rhEGF.
- Box x 6 vials containing 75 µg of lyophilized rhEGF.

Instruction for use, handling and disposal:
- Use each vial of **Heberprot-P®** for same patient only.
- Be careful to avoid deteriorations and bacterial contamination of the vials.
- Wash hands properly and wear sterile gloves before manipulating and applying **Heberprot-P®**.
- Care must be taken to avoid disseminating germs at the lesions. Change of needle is recommended when injecting different parts of the lesion.
- Once the treatment is ended, it is necessary to discard the remaining product.
- **Heberprot-P®** must be kept always in its original sealed packing.
- Keep out of reach of children.

The use of **Heberprot-P®** to treat diabetic foot ulcers under the current clinical practice has shown similar positive results to the previous data described at the clinical patient's evolution records and the dossier containing **Heberprot-P®** drug safety information.

REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas, 9th edn. Brussels, Belgium: 2019. Available at: https://www.diabetesatlas.org.

2. The International Working Group on the Diabetic Foot. Practical guidelines on the prevention and management of diabetic foot disease. Available in https://iwgdfguidelines.org/wp-content/uploads/2019/05/IWGDF-Guidelines-2019.pdf.

3. Berlanga-Acosta J, et al. (2015) Torpid Diabetic Wound Healing: Evidence on the Role of Epigenetic Forces. Int J Diabetes Clin Res 2015;2:1.

4. López-Saura, et al. Medical Practice Confirms Clinical Trial Results of the Use of Intralesional Human Recombinant Epidermal Growth Factor in Advanced Diabetic Foot Ulcers. Adv Pharmacoepidem Drug Safety 2013;2:2

5. Yera-Alos, et al. Active post-marketing surveillance of the intralesional administration of human recombinant epidermal growth factor in diabetic foot ulcers. BMC Pharmacology and Toxicology 2013;14:44.

6. Sun JZ, Lu Y, Xu Y, Liu F, li FQ, et al. Epidermal growth factor receptor expression in acute myelogenous leukaemia is associated with clinical prognosis. Hematol Oncol. 2012;30(2):89-97.

7. Berlanga-Acosta J. Diabetic lower extremity wounds: the rationale for growth factors-based infiltration treatment. Int Wound J 2011;8:612-20.

8. Fernández-Montequín JI, et al. Intra-lesional injections of recombinant human epidermal growth factor promote granulation and healing in advanced diabetic foot ulcers: multicenter, randomised, placebo-controlled, double-blind study. Int Wound J 2009; 6(6):432-43.

9. Fernández-Montequín JI, et al. Intralesional administration of epidermal growth factor-based formulation (Heberprot-P) in chronic diabetic foot ulcer: treatment up to complete wound closure. Int Wound J. 2009;6(1):67-72.

10. Berlanga-Acosta J, et al. The pro-inflammatory environment in recalcitrant diabetic foot wounds. Int Wound J 2008;5(4):530-9.

11. Baxley LA, Guilick WJ. The epidermal Growth Factor Family. Endocr Relat Cancer 2005 Jul;12 Suppl 1:S17-27.

12. Imperatore G, Cadwell BL, Geiss L, et al. Thirty-year trends in cardiovascular risk factor levels among U.S. adults with diabetes: National Health and Nutrition Examination Surveys, 1971-2000. Am J Epidemiol 2004;160(6):531-9.

13. Engelgau MM, Geiss LS, Saaddine JB, et al. The evolving diabetes burden in the United States. Ann Intern Med 2004;140(11):945-50.

14. Honeycutt AA, Boyle JP, Broglio KR, et al. A dynamic Markov model for forecasting diabetes prevalence in the United States through 2050. Health Care Manag Sci 2003;6(3):155-64.

15. Falanga V, Eaglstein WH, Bucalo B, Katz MH, Harris B, Carson P. Topical use of human recombinant epidermal growth factor (h-EGF) in venous ulcers. J Dermatol Surg Oncol 1992;18(7):604-6.

16. Falanga V. Growth Factors and Chronic Wounds: The Need to Understand the Microenvironment. J Dermatol 1992; 19(11):667-72.

17. Cohen S. Isolation of a mouse submaxillary gland protein accelerating incisor eruption and eyelid opening in the new-born animal. J Biol Chem 1962;237:1555-62.